

REMARKS

Pursuant to the Examiner's request Applicants have amended the and updated the specification concerning related cases. No new matter has been added by virtue of these amendments and entry is respectfully requested.

The undersigned and Dr. Moses would like to thanks Examiner Gitomer for the courtesies extended during the May 20, 2004 interview. The substance of the interview is set forth in form PTOL-413.

Claims 130, 149-180 are rejected under 35 U.S.C. 103(a) as being anticipated over the combination of Howard in view of Davies.

Applicants respectfully disagree and submit that this rejection be withdrawn for the following reasons.

The present invention is directed to a non-invasive method for facilitating the diagnosis of cancer of an epithelial origin, by obtaining a urine sample from a subject; detecting the presence or absence of a matrix metalloproteinase in the urine sample; wherein a matrix metalloproteinase in the urine sample is indicative of a cancer of an epithelial origin.

The methods of the present invention have important advantages over other accepted markers. First, the methods of the present invention are **non-invasive**. Unlike currently used tumor markers, e.g., PSA, CA 125 and CEA, which require a blood sample, all that is required with the present invention is a urine sample. Additionally, the sensitivity and specificity of the claimed methods are comparable to, or better than, those observed for current medically accepted cancer markers PSA, CA 125 and CEA.

Secondly, unlike the currently used tumor markers, that only detect one type of cancer, the methods of the present invention can screen for the presence of all cancers of epithelial origin. If the MMP screen is positive, the physician can then order more invasive and expensive tests in order to identify the particular cancer and pinpoint its location. Thus, the invention not only provides an increased likelihood of detecting cancer early, when it is most treatable, it saves healthcare dollars by avoiding the initial use of expensive procedures for screening purposes. Additionally, the noninvasive nature of the present screen will encourage more people to be screened and, thus, increase the likelihood of detecting cancer earlier.

The cited references, alone or in combination, do not teach or suggest the claimed invention.

According to the action, Howard et al teaches that "MMP's correlate their presence with different stages of bladder cancer." Applicants respectfully disagree.

Howard et al., is an approximately 116 word abstract¹ in which the authors discuss their attempt to investigate "the possibility of correlating their [MMPs] presence in urine with different stages of bladder cancer (Howard et al., lines 6-8)." However, what Howard et al., reported was **not** a correlation between MMPs in urine and cancer but that a "**striking variation** existed in the sample population (emphasis added, Howard et al., lines 12-13)." In other words, no correlation was shown. Thus, Howard et al., not only does not teach that the presence of an MMP in urine is diagnostic but, by teaching that there was a "striking variation" between MMPs in urine and cancer, actually would direct one skilled in the art away from the claimed invention.

Davies et al., the secondary reference, does not make up for this deficiency. Davies is a traditional invasive approach that looks at MMP expression in **tumor biopsies**, not in urine samples. Moreover, Davies is looking a different criteria than the present method. When Davies et al., looked at MMP levels, they found higher levels of MMP-9 and MMP-2 in transitional cell carcinoma (TCC) of the bladder. Yet, when Davies look at MMP expression, *per se*, not level of expression, they found that **57%** of normal bladder biopsies expressed MMP-9, while **76%** of bladder tumor biopsies expressed MMP-9 (page 5367, column 2, lines 1-5). Thus, looking at expression only does not teach anything according to Davies, because Davies teaches that the presence of MMP-9 in a biopsy is **not** specifically selective of cancer.

Applicants respectfully submit that the combination of Howard et al and Davies et al would not have directed one skilled in the art to assay MMPs in urine to detect epithelial cancers. Thus, the rejection should be withdrawn.

CONCLUSION

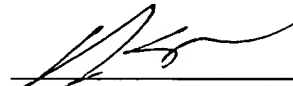
In view of the above and foregoing, it is respectfully submitted that the claims now on file are believed to be in condition for allowance, and prompt and favorable action is earnestly solicited. Should there be any question concerning this response or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

¹ A search of the literature did not uncover a full length paper related to this abstract.

Authorization is hereby given to the Commissioner to charge any deficient fees or to credit any overpayment to account no. 50-0850.

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Respectfully submitted,



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